An investigation of the factors effecting high-risk individuals' decision-making about prophylactic total gastrectomy and surveillance for hereditary diffuse gastric cancer (HDGC)

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Abstract

Hereditary Diffuse Gastric Cancer (HDGC) has an early onset and poor prognosis, therefore, individuals who carry a pathogenic (*CDH1)* mutation in the *E-cadherin* gene (*CDH1*) are offered endoscopic surveillance and advised to undergo prophylactic total gastrectomy (PTG) in their early to mid-twenties. Patients not ready or fit to undergo gastrectomy, or in whom the genetic testing result is unknown or ambiguous, are offered surveillance. Little is known about the factors that influence decisions to undergo or decline PTG, making it difficult to provide optimal support for those facing these decisions. Qualitative interviews were carried out with 35 high-risk individuals from the Familial Gastric Cancer Study in the UK. Twenty-seven had previously undergone PTG and eight had been identified as carrying a pathogenic *CDH1* mutation but had declined surgery at the time of interview. The interviews explored the experience of decision-making and factors influencing risk-management decisions. The data suggest that decisions to proceed with PTG are influenced by a number of potentially competing factors: objective risk confirmation by genetic testing and/or receiving a positive biopsy; perceived familial cancer burden and associated risk perceptions; perceptions of post-surgical life; an increasing inability to tolerate endoscopic procedures; a concern that surveillance could miss a cancer developing and individual's life stage. These findings have implications for advising this patient group.

Key words

Hereditary diffuse gastric cancer (HDGC): prophylactic gastrectomy: decision-making: psychosocial: *E-cadherin* (*CDH1*): endoscopic surveillance

Introduction

Between 1-3% of gastric cancers are thought to be caused by highly penetrant dominantly inherited genetic mutations, this includes Hereditary Diffuse Gastric Cancer (HDGC) [1]. Between 25%-30% of cases of HDGC are caused by mutations in the *E-cadherin* gene (*CDH1*) [2-4]. *CDH1* mutation carriers have an earlier than average age of disease onset, with most cancers occurring before 40 years (mean 38y range 14-69y) [5,6]. HDGC is not fully penetrant, and cancer risks are sex-linked; cumulative risks of gastric cancer at 80 years are 70% in men and 56% in women, and women also have a 42% risk of lobular breast cancer [6].

Because diffuse gastric cancer is often asymptomatic until in its advanced stages, the diagnosis is often delayed and, as a result, the prognosis is poor (the mortality risk is >80%) [7,8]. This can be particularly problematic in younger patients for whom cancer is thought to be unlikely [9]. The result is that at-risk individuals, are faced with making decisions about how/if to reduce their cancer risk. Those identified as at high-risk, as a result of genetic testing, are strongly advised to consider undergoing prophylactic total gastrectomy (PTG) in their early twenties [1, 10].

Surveillance, using endoscopy and/or chromoendoscopy plus multiple random biopsies, has an important role to play for individuals awaiting genetic test results or who are not psychologically ready or physically fit for a gastrectomy [1, 10]. Moreover, positive biopsy results generated during surveillance may also be used to inform surgical decision-making [11]. With regard to the risks of other cancers, women with a pathogenic *CDH1* mutation are recommended to undergo annual bilateral breast MRI, which can be combined with mammography, from 30

years of age [1,4-5,12]. Annual colonoscopy is recommended for individuals in families in which colorectal cancer is reported in *CDH1* mutation carriers [1, 10].

Gastrectomy carries a 100% long-term morbidity risk [7]. After-effects of surgery include: rapid intestinal transit; weight loss (>20% of body weight); dumping syndrome; diarrhoea [1, 7, 13-15] and iron deficiency anaemia and osteoporosis, which is particularly serious in women [1,4], all of which have may have serious physical and psychosocial implications. While long-term morbidity and mortality data for PTG are unavailable, histological examination following this procedure indicates the presence of occult cancers in the gastric submucosa in the majority of *CDH1* carriers [11,13, 16-18] however, whether these would have progressed to invasive carcinoma is unknown [5,8,17]. The optimal timing for PTG is therefore, unclear, but it is suggested that it should be offered in early adulthood as the risk of gastric cancer death exceeds risk of mortality from surgery in the mid-twenties [1, 4,8,11].

There has been no systematic attempt to study the factors affecting decisions to undergo PTG. Anecdotal accounts and case reports of *CDH1* testing suggest that anxiety about developing cancer; worry about long-term impact of surgery on quality of life and responsibility to family and others influence surgical decisions [13,19-20] There is evidence that mutation carriers are generally satisfied with their decision to have PTG [13]. Lynch et al., [13] report that those who refuse surgery cite as reasons: variable age of disease onset/no disease in *CDH1* carriers; the potential negative impact upon employment, family life and insurance status; confidence in surveillance and regarding surgery as too extreme. Others report that pre-existing co-morbidities or concerns over fertility; cultural and religious beliefs and worry about loss of earnings also result in a decision to delay surgery [11]. If we are to

provide high-risk patients with the care that they require, then we must acknowledge there is a pressing need for in-depth research that determines (potential) *CDH1* carriers' understanding of their risk status and the factors influencing their risk management decisions. This paper reports the findings of an interview study that sought to determine individuals' experiences of, and views about, risk management for HDGC. The data reported below focus on risk management decision-making in high-risk individuals.

Design and Methods

This qualitative interview study included two groups of high-risk individuals sampled according to confirmation of their carrier status **and** whether they had undergone surgery or were continuing surveillance.

• Group One (**surgery**) individuals who have previously undergone PTG.

• Group Two (**surveillance**) *CDH1* mutation confirmed undergoing surveillance.

Recruitment

Members of the UK's *Familial Gastric Cancer Study* (FGCS) who were aged >18 years and who met the above study criteria were sent a recruitment pack. This included: an invitation letter from Consultant/FGCS Coordinator, information leaflet and an opt-out form to return directly to SB/NH. If the recipient did not opt out within three weeks, the researchers contacted them to arrange an interview.

Data collection and analysis

Data were collected in face-face interviews carried out by SB or NH. The interview guide focussed upon: risk perception; views about surveillance and PTG; experiences of DNA testing; factors involved in decision-making; information needs and, for those

who had undergone surgery, the physical, emotional, social and economic impact of PTG. The study employed an emergent design, which entailed simultaneous data collection and analysis, with the result that the ongoing analysis formed the basis of targeted questioning in later interviews.

Interviews were audio-recorded and transcribed. A conceptual framework for indexing and analysing data was developed using the method of constant comparison [21]; this enabled the identification of recurrent themes between and within interviews. Transcripts were anonymised, allocated pseudonyms, read and coded by members of the research team. NH, JL and SB discussed emerging findings while analysis was ongoing. Data were examined for negative evidence to counteract the possibility of researcher bias. The analysis reported below focuses upon the processes of, and influences on, risk management decision-making.

Results

Participant characteristics

Forty-two FGCS participants from the FGCS who had already undergone PTG or had been confirmed as carrying a *CDH1* mutation and were currently undergoing surveillance were approached; two declined and five were unavailable for interview. Thirty-five (83%) individuals from 14 families were recruited. The number interviewed per family ranged from 1- 4 individuals.

With regard to risk management (See Table 1), 27/35 (77%) interviewees had undergone PTG between 0.5-9 years previously (median 3 years). Interviewees' age at surgery was between 19 and 64 years (median 36 years, mode 26 years). Thirty two (91%) interviewees had undergone DNA testing and were confirmed as carrying

a pathogenic *CDH1* mutation. Twenty-three (85%) of the interviewees in the surgery group had had their mutation carrier status confirmed before undergoing PTG, one (4%) following surgery and three (11%), who had already had surgery, still had to undergo DNA testing. Eight (23%) interviewees were currently having annual surveillance, all were confirmed *CDH1* mutation carriers and had discussed PTG with healthcare providers, one was awaiting surgery at the time of the interview. The interviewees came from various centres in the UK. In some cases their surveillance or surgery was carried out locally, others were managed in Cambridge as part of a tertiary referral service.

Sixteen(59%) interviewees had received a positive biopsy following endoscopy, 13 (48%) had undergone PTG as a result, so it could be argued that surgery in these cases was "semi-prophylactic"[9], indeed, some of these interviewees interpreted a positive biopsy as confirmation of malignancy. Two of the three interviewees undergoing surveillance who had received a positive biopsy result had opted to continue surveillance for the present, the other, as noted above, was about to have surgery.

Table 1 about here

When reflecting upon their experiences of managing their cancer risks interviewees talked about both the processes of decision-making and the influences on their decisions. We will begin by describing how the dynamics of decision-making were experienced and then go on to outline the factors that interviewees described as influencing risk management decisions.

Experiencing decision-making

How are risk management decisions experienced? Given their family history, a few interviewees regarded their decision to undergo PGT as predetermined, given the magnitude of their risks:

Rosa: in my eyes we didn't have any choice. So I've had no choice over any of it, really. So that's why I've kind of taken it [PTG] in my stride, it's not like I had the choice of this or this, it was this or nothing, kind of thing. So the choices had already been kind of given to us. *(Surgery)*

The remaining interviewees in the surgery group described surgical decision-making as a relatively easy choice, for example, Larry said it was "..a *big decision but I don't think it was that hard"*. Although all perceived the decision to have PTG as potentially life-changing (see below), for many of those who had undergone surgery it was described as a relatively straightforward decision to make: *"It was just a no-brainer really." (Joel).*

Some interviewees said that they had made the decision to have PTG easily and relatively quickly, whereas others described surgical decision-making as a more difficult and complex process, which had taken place over a long period of time.

Maya: And it was too much pressure and it was too big a decision to make. It just felt like I was giving up too much. I was thinking, you know, I just couldn't handle going through surgery…it just seemed really extreme to me. (Surgery)

No matter how individuals presented the process of surgical decision-making – quick vs. protracted, straightforward vs. complex – risk management decisions appeared to be influenced by a number of competing clinical, emotional, personal and social factors, which are explored below.

Objective confirmation of cancer risks

Establishing that one carries a pathogenic *CDH1* mutation was seen as an integral part of the decision-making process by some interviewees. As Erica *(Surgery)* commented about her genetic test result: "*I said from the beginning if it was positive then I would go and have the operation".* Anna voiced similar sentiments: *"Yeah, so I had the gene. And then I made that decision like, I think I had the results and six weeks later I had the surgery. I kind of wanted it over and done with." (Surgery)*

While confirmation of one's *CDH1* carrier status acted as an immediate trigger for surgery for a small group, for approximately half the surgical group, receiving a positive biopsy had been the necessary step in their surgical decision-making. This included Keira who described her reaction to the news that they had detected cellular changes in her and her brother's biopsies as follows:

Keira: I instantly thought, well that means we'll have to have surgery. Because I wouldn't risk, um, not having surgery. I wouldn't take that risk of living life kind of on, not on the edge but just always thinking you know, oh it could turn into something nasty. So I instantly knew from the phone call that we were going to have surgery. (Surgery)

While many interviewees understood a positive biopsy as signalling the presence of a precancerous lesion, they said that living with the knowledge that their cells were already changing was too anxiety provoking, hence their decision to proceed to surgery following this result.

Marion: I mean, once you have been diagnosed with these cells you sort of feel, you know, "oh, when is…?" you know, it's probably in your brain every day, isn't it? You know: "has it started?" or… Or any twinge of discomfort, you're thinking… So it's easier to have the stomach removed really. (Surgery)

Others, like Richard, described how they had interpreted a positive screening result as confirmation of a cancer, which resulted in their decision to have PTG immediately: *"For me my stomach was about to become a big cancer bomb… I just thought my stomach had cancer because they found stuff." (Surgery)*

Finally, a number of those in the surveillance group said that if they were to receive a positive biopsy in the future, then they too would have PTG.

Josh: Just go through the screening. If it comes back positive look at the options that are available, which only seems to be really one option [PTG], and then manage your life based on the outcome of that, in a sort of planned fashion. (Surveillance)

Objective confirmation of one's cancer risks by genotyping or biopsy can thus, be seen important triggers for PTG, however, there were a number of subjective factors, which also influenced risk management decisions. First, as the next section demonstrates, prior experiences of cancer within the family - the familial cancer burden- were regarded as crucial in determining individuals' views of the different risk management options.

Familial cancer burden

All interviewees said their experiences with cancer in their family had motivated them to consider PTG. Many had seen close relatives diagnosed and die from stomach cancer, and described how this had directly influenced their anxiety about cancer risks and, hence, their decision to manage their risks by undergoing PTG.

Colleen: I'd already discussed beforehand that if I had got it [mutation] then I think I would have my stomach removed because of the way my sister died and everything that happened to her, I did not want to go through that. … and my dad was like a

skeleton, from a big man to a skeleton before he died, and it was horrendous, and everything he went through was horrendous. (Surgery)

Some said that the emotional and biological closeness of the relationship or the amount of direct experience they had had with relatives during their illness had been, or would be, important influences on surgical decisions.

Phoebe: I know that if Mum [CDH1 carrier + PTG] had died then I'd have a very, very different view towards all of this. So I think it really does kind of affect you sort of knowing who has died in your family and if it's immediate, I mean, I was very close to [uncle] obviously and it affected me quite a bit but I think, your parents are your parents, aren't they? So, yeah, I think that must have a massive effect on people's decision-making processes. (Surveillance)

However, it was not only a relative receiving a cancer diagnosis or witnessing a family member's death that was cited as influencing surgical decision-making, but also a family member testing positive at screening or undergoing PTG. For example, Maya said that once her sister had received a positive biopsy result she knew that she had to proceed with surgery also.

Maya: I hadn't quite decided, to be honest I was quite against it [PTG] I didn't really want it. Just because I think I didn't want the change, and the surgery, it just seemed really extreme to me. It was when my sister got cancer that was the turning point for me, and I felt like, yeah, I've really got to get it done, I can't just ignore it, it's bound to affect me. (Surgery)

As these data suggest, interviewees' prior experiences of cancer within the family can be seen as an important factor in risk-management decisions not least, because they influence individuals' perceptions of their own cancer risks.

Risk perception and tolerance of uncertainty

Many interviewees talked about their fears of developing cancer and drew upon tried and trusted metaphors when describing their cancer risks. "*So the more I spoke about it with my wife, we couldn't rest thinking that I was sort of this ticking time bomb" (Louis).*

All interviewees described their risk of developing stomach cancer as high. For some the risk of cancer was described as a certainty and they said that this perception had directly influenced their decision to have PTG:

Nico: … having the operation by the time it was even on offer I was pretty certain more or less, looking at my family history and the rest of it, I wasn't going to last that much longer anyway. So it wasn't much of a decision, really. (Surgery)

Both individuals who had already undergone PTG and those who were having annual surveillance described living with the risk of stomach cancer as anxiety provoking.

Sami: I am a bit of a worrier, and … I'll be honest, since I had the test done it has, it's [cancer] always there. You're just constantly thinking. And because my dad passed away when he was young as well … you sort of do worry. (Surveillance)

Risk perception, and the fear and anxiety it may generate, was related to interviewees' views about the speed of spread of disease "*it's [cancer] so clever and quick"(Erica, Surgery)* and its lack of detectability: *"80% is too big a risk for me. And knowing that the screening's not effective, and knowing how quickly it spreads as well, I couldn't take that chance." (Rani, Surgery)*

Interviewees' anxiety appeared to be related to what they perceived as the fundamental uncertainties of stomach cancer; namely, if and/or when it might develop.

Int: What do you think the main impact is for you at the moment, in terms of the genetic diagnosis?

Sami: Just not knowing. Just having to live every day just not knowing what's going on inside your body. It might sound weird. You just worry all the time. You know, if I get like a twinge in my stomach or, I just think, oh my God, what's this? (Surveillance)

While, in some cases their inability to tolerate uncertainty led interviewees to opt for PTG, others said that uncertainty about the occurrence or development of cancer had influenced their decision to postpone surgery for the present, although, as noted above, the majority of interviewees in the surveillance group said they would opt for PTG in the future if they received a positive biopsy result or a cancer developed. As Giles said: *"I'll carry on having screening, and then should … um … you know, something significant happen then I'll have a gastrectomy." (Surveillance)*

Uncertainty about cancer occurrence was not the only type of uncertainty discussed by interviewees, as the next section demonstrates, many of those who were continuing with surveillance said they had rejected the surgical option for the present because of uncertainty about the surgical outcomes.

Perceptions of a post-gastrectomy life

One of the problems for healthcare professionals when advising patients about whether or not to undergo PTG is that it is difficult to predict how individuals will adapt to gastrectomy and how it will impact on their health and wellbeing, given the wide range of surgical outcomes. Our interviewees were aware of medical uncertainty about surgical outcomes, indeed, some of those who rejected PTG justified their decision on these grounds.

Sami: you don't know how important your stomach is. I mean it must be an important part of your body and there is a lot of side effects to having it done, it just affects your whole life as well, really, so I didn't choose to do that. (Surveillance)

Interviewees in both the surgical and surveillance groups described how risk management decisions were influenced by their worries about living without a stomach and the potentially negative impact on their ability to work, care and provide for a family, socialize and lead an active life. This included Angus, who had undergone PTG following a positive biopsy result and who described how he felt prior to his surgery:

Angus: And I still thought "well, I don't want an operation because I want to be able to do my football and stuff like that, I want to go and do stuff, and I feel fine and I was concerned about the impact on my lifestyle, right. Because I enjoyed my sport, I enjoyed playing at football, you know, my cycling, my running, all that sort of…(Surgery)

All interviewees were aware that surgery would result in major life changes. While some had found this information on the Internet, via patient support groups, or through talking to healthcare professionals, others described having witnessed other family members adapt to life post surgery. Many interviewees described how they had watched relatives struggle with: eating; maintaining their weight; fatigue and dumping syndrome post surgery, and said that this had clearly influenced their surgical decisions. Joe, a *CDH1* carrier, who had watched his sister strive to maintain her weight post surgery, said that he had postponed PTG for a number of years because he had been worried about how weight loss might impact on his social life and earning potential.

Joe: why do something that you might not need? Because I think in my head there was that possibility. … I thought "screening – there's a possibility I could get away with it" – that's the way I live my life! Because I still had that thought about "if I get this op' my life's over; I'm going to lose loads of weight, I'm going to lose strength, I won't be able to play drums", that was my biggest fear, …The whole idea of you don't have a stomach, you've got to change the way you eat, the way you drink, the way you take in nutrients and how your body processes them. (Surgery)

Another *CDH1* mutation carrier, Alana, who had received a positive biopsy but had decided against PTG, said her aunt's post-surgical experiences had put her off proceeding with surgery for the present.

Alana: my aunt, she's had her stomach removed. But she's had a really, really bad experience with it, …the reason I think I've got such a negative experience of getting the stomach removed is because it's completely changed her life, it's completely, it really has changed her life. She's socially, she can't go out very much, she's constantly ill, she's still being sick. (Surveillance)

However, observing relatives was not always seen as a deterrent. Some interviewees described their relatives as positive surgical role models, and said that seeing how easily or quickly their relatives had adapted to life without a stomach provided the final impetus for them to proceed with surgery. Maya, for example, described how witnessing her sister's recovery trajectory had positively affected her views of PTG.

Maya: so at first I was thinking I just couldn't handle going through surgery, but I think watching my sister go through it as well, and seeing how well she coped that was helpful for me because then it made me feel more like, OK, maybe I would be

able to cope with it. Plus it … the bonus of having her getting the surgery done first was that I got to learn about the worst parts of the surgery and try and find ways to accommodate it where I didn't feel scared to go in. …I think if you actually see it yourself first hand as well, you know what you can and can't cope with, and what's going to be difficult for you. (Surgery)

It was not only their perceptions of PTG that shaped interviewees' risk-management decisions, all interviewees said their feelings about endoscopic surveillance were very influential when it came to deciding whether and when to proceed with surgery.

Experiences and perceptions of endoscopic surveillance

Many interviewees in both the surgery and surveillance groups described surveillance as anxiety provoking. Some said they (had) experienced increasing anxiety in the lead up to endoscopy appointments, while others said that waiting for the results was a source of worry.

Phoebe: it's all very well kind of saying it's only once a year but actually it's not really because you've kind of got that whole afterwards, a month of waiting and that month is often quite, you know, difficult. (Surveillance)

In addition to the emotional toll of undergoing surveillance, endoscopic screening and biopsy were also described as physically uncomfortable by most interviewees. Indeed, some said their growing fear and dislike of endoscopy had played a crucial role in their eventual decision to opt for PTG.

Rani: and the endoscopies were quite traumatic as well, because I had one done and I woke up in the middle of the procedure, and… I wasn't aware of what was

happening so yeah, I wouldn't want to have to go through that for the rest of my life … (Surgery)

Surveillance was also seen as time consuming, and some said their busy work schedules had meant that attending screening appointments in (tertiary referral) centres that were far away from home had become increasingly difficult:

Joe: It's frustrating because it gets in the way of your life…and having to take time off working …Like I said, I found it more and more difficult so I had to have someone with me [and]I didn't like asking people to take me. And I lived quite far away from wherever I was getting them done and I preferred just to drive there myself, anti-gag, get it done, Bob's your uncle, I can go home. (Surgery)

While the inconvenience of, and/or an increasing inability to tolerate, endoscopy had led some individuals to opt for PTG, many of those who had undergone surgery said they had come to the realisation that surveillance might not detect a malignancy until it is too late and, therefore, had perceived endoscopy as unreliable. Growing concerns about their risk of developing cancer, despite undergoing endoscopy, had meant that some interviewees had eventually decided to proceed with surgery, even though their biopsies were clear.

Angus: I think screening can give you false assurances. And that's certainly what my gastroenterologist was concerned about "every time I come back and say you're negative it's because the bits I've actually picked up…" actually I didn't realise it [screening] was just, you know, a lucky-dip-type thing almost. Because of this cancer, because of the way it spreads. (Surgery)

Others said they were so concerned about their risk that they had proceeded straight to surgery once they had their risks of developing cancer confirmed by DNA testing.

Sylvia: And I just thought to myself, your stomach is large, this cancer grows in layers, how can they find it? They've only got to miss it once and then you've got another six months of the cells dividing, …I looked at the stats and all the percentages and I thought, what would be the point of having an endoscopy? (Surgery)

The majority in the surveillance group was aware that surveillance biopsies could miss cellular changes, but nonetheless, perceived surveillance as providing them with a limited form of security for the present.

Phoebe:…the decision to kind of go and start that surveillance was easy for me because it was too much of a risk not knowing anything and it kind of gives you a little bit of comfort knowing that. Even though they do say that they're really taking small biopsies of what is effectively a massive organ [and] you never really know whether they're going to miss it or whatever (Surveillance)

To summarise, as the above analysis suggests, risk management decisions are influenced by a number of personal and social factors. However, for most of our interviewees the most difficult decision they faced was not whether to undergo PTG, but when they should have this procedure. Thus, timing can be seen as one of the most important considerations when managing the risk of stomach cancer.

Timing of surgical procedures

Phoebe: there's never a good time to make the decision to have the endoscopies, there's never a good time to make the decision to have surgery because no matter

what, you'll deal with it in your own way, sort of it depends very much on who you are as a person. (Surveillance)

While, as Phoebe commented, there may never be a "good time" to have surgery, for most interviewees there was definitely a right time. As indicated above, for approximately 50% of the surgical group the right time had been when they had received a positive biopsy. For many of the remaining interviewees the timing of surgery was related to their life stage. Some said that once they had established they carried a mutation they had decided to have surgery in their twenties because they were young, fit and more physically resilient. Others said that choosing to undergo surgery when young(er) was easy because one has fewer social responsibilities, including*: "full-time jobs, children and mortgages"* (Anna).

However, some of those in the surveillance group who were in their early twenties said their age acted as a deterrent when it came to surgery, they said that undergoing PTG at this time in their lives would negatively impact their perceived life trajectory and interfere with their career ambitions.

Perran: Because my parents make it out to be, 'Oh, just, you know, you have your, chop your stomach up, choppity-chop and off the chopping block and you're back to life.' It's not like, it's six months out of my life I've got to take out for this, and it's, you know, it stops me progressing quite a lot. (Surveillance)

These interviewees saw PTG as a disruptive life event, and said they preferred to wait until they were older, had enjoyed a carefree youth and achieved some of their life goals - finding a partner, having children, establishing a career - before proceeding with surgery.

Alannah: I'm in my early 20s, I want to go out drinking and go out eat[ing]-, like go out for meals with family and friends, and live life normally… I don't want it[PTG] to affect my life, I want to be able to live through my 20s at least like happily … as a young 20 year old should do, type thing. And looking ahead I don't know whether I want children before I have it done.(Surveillance)

Phoebe: it makes me think about my future quite a bit because I often think, you know "at what stage would I elect to have the surgery if they were to find cancerous cells and how would that affect meeting new people and how would that affect kind of having children and at what stage do I want to kind of start making these decisions? (Surveillance)

Many interviewees who had undergone surgery when they were older (>30 years) said their risk management decisions had been influenced by the fact that they were already parents. A large proportion of those in the surgery group who had children said they had felt they had a responsibility to manage their risks surgically for their family's sake. This had stemmed from a desire to remain healthy and secure their future so they could raise and care for their children:

Kay: I just felt very much, I had three young children, I needed, as a mother, to be there for them, I wanted to be there for them and be part of their lives and see them grow up. (Surgery)

Others said that they had had PTG so that their children would not have to watch them suffer or to prevent family members from suffering a(nother) bereavement. As Nathan commented: "*What I didn't want to do is think, if you look*

at my 12 year old son, I didn't want him then to think, hang on, I haven't got my dad in two years.". (Surgery)

Finally, a couple of interviewees in the surveillance group said that the timing of risk management was not related to their age, but to their current health status; they had a range of comorbidities, which meant they were not good surgical candidates at present. Both acknowledged that if their health changed, then they would consider PTG in the future.

Alastair: as time goes on I know there's an egg timer turned upside down and it's ticking away. And I know at some stage along this route that it's highly, highly probably that I'm going to have to have this surgery….if they come back and say, 'Yeah, we've found a cluster of cells,' or 'There's a significant change in the way that your gastric lining is looking for us to suspect that something is there,' then you know, that'll make things a lot clearer for me. (Surveillance)

Discussion

This paper reports the findings of one of the first systematic studies of decision-making about surgical risk management for HDGC. Our data suggest that decisions to proceed with PTG or continue with surveillance (endoscopic screening and biopsy) are influenced by a number of different and interrelated factors: objective risk confirmation, perceived familial cancer burden, subjective risk perceptions, experiences and perceptions of the different risk management options and life stage.

Decision-making about risk management was described as a fluid or dynamic process. Some individuals presented surgical decision-making as relatively quick and straightforward, while others portrayed it as difficult and complex and as taking

place over a period of time [13]. These observations resonate with the findings of studies of individuals who are at risk of Familial Adenomatous Polyposis (FAP), which suggest that decision-making about prophylactic surgery is protracted in some cases while, in others, it is described as a relatively rapid process [22-23].

It is suggested that the speed of decision-making may be related to the fact that some interviewees have definite thresholds or triggers for surgical risk management, for example, a positive genetic test result or a positive biopsy. Similar observations have been made by Garland et al., [19], who report a series of case studies of patients undergoing gastrectomy for prophylactic and palliative reasons and suggest that surgical decisions are primarily prompted by a triggering event; specifically, a relative dying from gastric cancer, having a positive biopsy result or receiving a diagnosis of metastatic disease. The impact of objective confirmation of cancer risks on surgical decision-making has also been observed in carriers of other highly penetrant dominantly inherited mutations which predispose to colorectal cancer (Lynch Syndrome and FAP) [22,24]. Collins et al. [24], observed high-risk individuals reporting an intention to undergo colectomy prior to having predictive testing for Lynch syndrome if they should be identified as carrying a mutation, however, they noted that none of those confirmed as carriers had acted upon these intentions twelve months later. This may be due to the greater perceived tolerability of colorectal screening procedures compared with gastric screening, or, alternatively, it may be an artefact of the relatively short follow-up period involved in Collins et al.'s study. In the case of FAP, because predictive genetic testing for FAP usually takes place in late childhood, it is the presence of screen-detected symptoms – polyps - which often precipitates a decision to undergo prophylactic colectomy,

rather than receiving a confirmatory genetic test result [22]. Our results, like those of Campos et al.[22], suggest that receiving a positive screening result is particularly influential when it comes to surgical decision-making, with approximately half of the surgical group undergoing PTG after receiving such a result. This observation confirms the positive role of surveillance outlined by Lim et al., who conclude that detailed targeted and random biopsies and histopathology can identify early lesions, which may facilitate informed decision-making about surgery in high-risk patients [11].

In addition to objective confirmation of risk, our data suggest that risk management decisions are also influenced by a range of subjective factors: perceptions of cancer burden and associated risk perceptions which have been reported previously as influencing decisions about breast/ovarian or colorectal cancer risk management in *BRCA1* and *BRCA2* [25-27], or Lynch syndrome [28] and FAP [23] mutation carriers, respectively. Our data suggest that family history of disease, particularly witnessing a relative's illness and death from gastric cancer, is a powerful incentive for surgery. In this respect our findings concur with case studies of surgical decision-making for HDGC, for example, Garland et al. report that one of their patients regarded his sister's death as the ultimate trigger for his decision to undergo PTG [19]. Similarly, Lynch et al. argue that growing awareness of the familial cancer burden was a particularly important determinant of risk perceptions and surgical decisions in one of their families in which eleven first cousins underwent PTG after receiving confirmation of their *CDH1* carrier status and witnessing a parent die of gastric cancer[13].

While risk perception and cancer burden may be important triggers for surgical decisions, our data suggest individuals' perceptions of surgical outcomes and attitudes about endoscopic screening are also very influential. Gastrectomy has some very obvious or visible consequences such as extreme weight loss, altered eating habits and fatigue [4], all of which may negatively affect individuals' ability to work, socialise or parent, and, thus, potentially impact individuals' quality of life post-surgery [19, 29-30]. Indeed, some of our interviewees reported that they had been deterred initially from undergoing PTG as a result of observing negative clinical and psychosocial *sequelae* in other family members. However, there was also some evidence that witnessing a positive post-surgical role model could overturn individuals' negative perceptions of post-surgical life, and this observation may have some implications for managing this patient group [1,13].

While surveillance and surgery are presented as available options or choices, the data suggest that few individuals actively choose surveillance to manage their risk of HDGC, rather, they engage in surveillance because they reject the option of surgery (at least for the present) (see also [13]). This may reflect the ways in which these options are currently presented within the clinic, for, it is currently emphasised that surveillance has a temporary, albeit important, role to play in the management of gene-positive individuals, insofar as it affords individuals some time to come to terms with their genetic diagnosis and to prepare for surgery [1,11]. Thus, with the exception of a small group who said they had proceeded straight to surgery upon learning they were at high risk, all our interviewees characterized surveillance as an interim measure until either they received some further form of confirmation of their risk from surveillance biopsies or they could no longer tolerate endoscopy

procedures. With regard to the latter, it must be noted that an inability to tolerate regular surveillance is not confined to HDGC patients. A number of studies of high risk patients undergoing colonoscopies to manage their risk of colorectal cancer suggest a small proportion are non-adherent, citing: embarrassment, pain, lack of sedation, time required off work and dislike of screening preparation procedures as reasons for failing to attend screening [22-23, 31].

It must be noted that *CDH1* mutation carriers' anxieties and concerns about the efficacy of surveillance, and their influence on surgical decisions have been reported previously. In a series of case studies of families with HDGC [13] Lynch et al. observe that 5/11 mutation carriers in one family reported increasing feelings of anxiety about the efficacy of endoscopy monitoring before they underwent PTG. Lynch et al. speculate that this may have been due to their counselling practices and the educational programme they provide for at-risk individuals, in which they emphasise the lack of knowledge about the effectiveness of endoscopy [13]. Indeed, there was some evidence in this study that interviewees' views of the efficacy of surveillance were influenced by information they had received from healthcare professionals and other sources (e.g. online patient support groups and other web-based information). Alternatively, it is possible that our interviewees' attitudes towards surveillance may have been influenced by the fact that some had undergone surveillance a number of years ago, when expertise in screening for HDGC was less common, or in a different centres, which are less skilled at identifying HDGC. Indeed, it must be noted that surveillance procedures have changed in recent years, and new guidelines, notably the Cambridge protocol, which recommend that

endoscopy should be carried out in centres of excellence, using skilled endoscopists/ histopatholgists, have only recently been published [1].

Finally, there was evidence that the timing of surgery was a really important consideration for our interviewees (see also [11]). As noted above, for the majority of interviewees, it was not a matter of whether to undergo surgery but when surgery should take place. Lynch et al, report similar findings, observing that several members of one of the families they studied commented "the only decision left [after confirmation of mutation status] was when prophylactic surgery should be performed" [13:2662]. While Lynch et al.'s patients all underwent PTG within a couple of years of receiving mutation results, the timing of surgery was a little more variable in our study. Although the majority of our interviewees who had undergone surgery had done so within a couple of years of receiving their mutation test result, some had delayed surgery for longer and approximately 25% had declined surgery when interviewed, despite receiving a positive mutation test result, in some cases up to six years earlier. These differences may be explained by the fact that the patients in Lynch et al.'s study were slightly older when they underwent surgery (39-61 years) and the majority already had children, whereas most of the interviewees who had postponed surgery and opted to temporarily continue surveillance in our study were: younger (<40 years), childless, had a complicating co-morbidity or were older than 60 years and perceived surveillance as a positive, albeit temporary, holding move while they prepared themselves for surgery. As noted above, as far as the younger interviewees in our study were concerned, their decision to undergo or postpone PTG had been or was influenced by their desire to establish and care for a family, to launch a career or continue working. The influence of age on surgical decision-

making has also been reported in patients undergoing prophylactic colectomy to manage their risk of FAP [22] and in carriers of *BRCA1* and *2* mutations who are considering risk-reducing bilateral salpingo oophorectomy (BSO) [32]. In all of these cases, age at surgery is, to a certain extent, determined by clinical factors - the degree of penetrance and the age of onset of disease - but psychosocial factors also play a role in the timing of surgery in these conditions. It has been observed that prophylactic colectomy is often delayed in young adults to accommodate patients' and family preferences, and education and career demands [22], while risk-reducing BSO, following the completion of child-bearing, is usually postponed until the early forties to avoid a prolonged (surgically induced) menopause [25].

Study strengths and limitations

To our knowledge this study is one of the first to systematically explore risk management decision-making in individuals who are at increased risk of HDGC. The fact that our sample included individuals who have undergone surgery at different time points can be seen as a particular strength because it allowed us to see whether changing clinical practices in the care of this patient group over the last decade have impacted on risk management decision-making. On the other hand, the fact that some interviewees had undergone surgery a relatively long time ago raises the possibility that their recall may have been affected. However, this is unlikely as there was no indication of any systematic differences between the accounts of individuals who had undergone more surgery recently and those who had made risk management decisions many years previously.

Clinical implications

What advice or help can we give those who are faced with making this decision? First, as we have described elsewhere [33-34], at-risk individuals need to be aware that life post surgery is very variable. There are few similarities between people in how they adapt to gastrectomy [1,13], so observing relatives' responses to surgery, and the impact it may have on their lives, may not be a good predictor for self and may set up unrealistic positive and negative expectations, which may bias decision-making. Recent guidelines suggest that when preparing patients for surgery they should be provided access to those who have already undergone PTG [1], this study endorses these recommendations and emphasises the need to ensure that those considering PTG are given the opportunity to engage with as many former surgical candidates as possible. Second, the interviews suggest that while surveillance may provide patients with time to come to terms with their risk status, finding foci of signet ring cells in endoscopic surveillance biopsies can trigger a decision to have surgery in some patients. Patients need to be carefully appraised about the role of endoscopy in risk management, so that they may make a timely and informed decision about surgery[1,8,11].

Conclusions

Individuals who are identified as at high risk of hereditary forms of gastric cancer either through their family history or as a result of mutation testing need to make decisions about managing their cancer risks, whether to undergo PTG or surveillance. This study suggests that risk management decisions are affected by a number of differing and potentially competing factors: receiving a positive mutation test result or positive biopsy result, perceptions of cancer burden, subjective risk

perceptions, experiences and perceptions of the different risk management options and individuals' stage in the life course. In order for healthcare professionals to support individuals in making these decisions, they need to be aware of the clinical, emotional, and social factors that influence cancer risk-management decisions.

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Conflict of Interest

NH, SB, JL,SR, RHH, RCF and CC declare they have no conflict of interest.

Ethics

Ethical approval for this study was given by Cambridge East Research Ethics Committee 14/03/2012 (Ref: 12/EE/0066). Informed consent was obtained from all

individual participants included in the study. The participants have been anonymised and allocated pseudonyms in this report.

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Table 1: Demographics, Family History and Risk management

Demographics (n=35)				
Gender	women: men	16	19	
Age at interview	mean:range	40	19-77	
Have children	yes:no	17	18	
Number of children	range	1-4		
Education	school:college:university	12	10	13
Reported Family History (n=35)				
Have: Total 1st degree relatives Gastric Cancer/+/PTG		35	109	
Have: Total 2nd degree relatives Gastric Cancer/+/PTG		28	76	
Have: Total 3rd degree Relatives Gastric Cancer/+ /PTG		22	47	
Range relatives PTG		0-3		
DNA Testing (n=32)				
Confirmed result		32		
No testing		3		
Age at DNA result (n=29)				
Median		20		
Range		18-75		
No data		3		
Years since DNA test (n=29)				
Median		4		
Range		1- ~9		
No data		3		
Risk management (n=35)				
Current surveillance		8		
Surgery		27		
No surveillance prior to surgery		6		
Years surveillance (n=29)				
Median		1		
Range		0-15		
Unsure/No data		4		
Biopsy positive (n=35)		**n=**	**%**	
Prior to surgery		13	37	
No surgery		3	9	
Age at surgery (n=27)				
<30 years		10	37	
<40 Years		6	22	
<50 years		7	26	
>51 years		4	15	

Years since surgery (n=27)		
<12 months	1	4
1-3 years	13	48
4-6 years	7	26
7-9 years	6	22